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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/004,427	12/06/2001	Subrahmanyam V. Yerramilli	044574-5003-2	8735

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/004,427	YERRAMILLI ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *06 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/02/02;1/30/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

Acknowledgement is made of Applicant's claim for priority based on Application No. 09/506,729, filed on February 18, 2000 (Patent No. 6,365,352), which claims priority to PCT application No. PCT/US98/17284, filed August 21, 1998, which claims priority to U.S. Provisional application No. 60/056,844, filed on August 22, 1997. It is noted that applicant has perfected the claim for priority by amending the Specification. (page 2 of the Transmittal of New Application). Application should amend the specification to indicate the present status of Application No. 09/506,729 (now US Patent No. 6,365,352). The pending claims are 14-36.

Specification

The disclosure is objected to because of the following informalities: There appear to be multiple references to nucleic acid sequences in the specification (pp. 14, 23-24 and 37-57). However, sequence identifiers are not properly used in any of the said references. On page 14, although the proper identifier is used (i.e. "SEQ ID NO:"), there are no numbers given. In all other instances identifiers are not used at all. See 37 CFR 1.821-1.825 and MPEP §§ 2421-2431. The requirement for a sequence listing applies to all sequences disclosed in a given application, whether the sequences are claimed or not. See MPEP § 2421.02. If said sequences were originally submitted in both electronic and paper format, then applicant is only required to make proper amendment to the Specification to include the appropriate SEQ ID NOs. However, if applicant has not previously submitted said sequences as part of the SEQ listing, then a new

submission is also required (i.e. CD-ROM/CD-R, paper copy and Attorney Statement concerning the SEQ listing). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. **Claim 14-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Base claims (14, 19 and 25) recite "A method of identifying an agent that modulates a sterile inflammatory disease". It is unclear what "modulat[ing] a...disease" encompasses. The specification is actually drawn to identifying agents that modify gene expression in a group of cells. However, the disclosure does not clarify what the metes and bounds are for "modulating" a disease. For example, does a change in the gene-expression-profile of a single gene equate to "modulating" a disease. As the term is not specifically defined and the disclosure contains references only as to the characteristics of gene expression modulation, the claims' metes and bounds remain indefinite.

Claims 14, 19 and 25 recites the limitation "the subject". There is insufficient antecedent basis for this limitation in the claim. This makes it unclear as to whether the "subject" of the latter part of the claim, whose gene expression profile is used as a reference, is necessarily the same individual as the "patient" from whom cells (e.g. granulocytes, polymorphonuclear white

blood cells) are isolated. It would be remedial to amend the claim to clearly indicate whether the "subject" and the "patient" are necessarily the same.

In addition, claims 14, 19 and 25 recite "comparing…at least one expression profile". It is unclear if the same genes are necessarily compared.

Claim 13 recites the phrase "ancillary reagents suitable for use". It is unclear what the term "suitable" encompasses, as it does not appear to be defined in the specification. Therefore, as written the claim's metes and bounds are indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Claims 14-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.**

The claims are drawn to methods of identifying an agent that modulates a sterile inflammatory disease in a patient or modulates glomerulonephritis in a patient, where granulocytes or polymorphonuclear leukocytes are isolated from the patient and treated with an agent with subsequent examination of a gene expression profile, which is compared to an expression profile from non-treated cells. The claims are drawn to the critical element of the expression profile necessarily correlating with a sterile inflammatory disease and that a change in

the expression profile for a gene or a combination of genes necessarily "modulates" (e.g treatment, exacerbation, amelioration, etc.) a sterile inflammatory disease (e.g. psoriasis, rheumatoid arthritis, etc.). As such the claims are drawn to a genus comprising a combination of genes, or for that matter to a single change, for which a given alteration in expression (i.e. up or down) necessarily correlates to "modulation". The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The teachings of the specification appear to be limited to preparation of expression profiles for granulocytes isolated from normal donor peripheral blood, where the cells are subsequently exposed to virulent and avirulent bacteria (*in vitro*), and a comparison is made of the expression profiles in the two groups of cells. (e.g. Spec. at p. 22, Example 1). In addition, the teachings disclose expression-profile comparison of neutrophils isolated from normal donor and a patient suffering from an undisclosed inflammatory disease. (Spec., pp. 57-58, Example 4). Thus, the specification does not actually provide identification of a gene or combination of genes, for which the expression profile is altered when cells are treated with a particular agent, resulting in "modulation" of a sterile inflammatory disease.

There are inflammatory disease-related genes that have been examined in tissue from patients suffering from inflammatory disease, such as rheumatoid arthritis. (e.g. Heller et al.

PNAS, 1997 March ; 94 :2150-55; see whole article; hereinafter Heller). For example, peripheral cDNA library has been used to identify genes expressed by lymphocytes infiltrating the inflamed tissues (i.e. in RA disease). (e.g. Heller, p. 2154, col. 2, ¶ 2). However, the art does not teach which gene(s) necessarily would lead to a modulation of disease in a patient, where isolated cells are treated with an agent *in vitro* to compare expression profiles to untreated cells.

In sum, given the enormous breadth of the genes or combination of genes for which expression profiles must correlated with an inflammatory disease, as encompassed by the rejected claims, and given the limited description from the instant specification of genes, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to described the broadly claimed genus for combination of genes. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species, because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

3. **Claim 14-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.**

The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir.

1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The claims are broad in scope and breadth, in that they are drawn to modulating any sterile inflammatory disease (e.g. base claim 14 and 19). In addition, even where the claims are more particular in the disease to be modulated in a patient (i.e. base claim 25; glomerulonephritis), the claims remain broad in that "modulation" of the disease can reasonably be dependent on alteration in expression profiles for an enormous number of or combinations of genes. Of course, where the claims are drawn to *any* sterile inflammatory disease, the claims are broader, simply because the genes or combination of genes would be reasonably deemed greater in number.

Nature of the invention. The invention embodies isolation of granulocyte cells, preparation of gene expression profiles from said cells, and treating cells to an agent and comparing expression profiles for treated and untreated cells, with the aim of identifying an agent that can modulate a sterile inflammatory disease in a patient.

State of the art/Unpredictability of the art. The state of art of modulating inflammatory diseases via agents that alter expression profiles (e.g. using microarray technology) for a gene or combination of genes is in a comparatively nascent stage of development. It is not difficult to compare expression profiles for a given group of cells, but it is a wholly different proposition to ascertain which genes when altered would necessarily correlate to modulation (e.g. amelioration or exacerbation) of inflammatory diseases *in vivo*.

For example, while genes may be identified as related to inflammatory diseases, such a determination does not necessarily translate into the conclusion that agents altering expression for such genes, would necessarily "modulate" sterile inflammatory diseases. (e.g. Heller et al. PNAS, 1997 March; 94:2150-2155; using microarray technology to compare expression profiles of certain genes in tissue extracted from patients suffering from sterile inflammatory diseases; see entire document). *A priori*, in order to determine which combination of genes when altered (e.g. up or down) necessarily correlates to "modulation" of a sterile inflammatory disease, in and of itself, would be unpredictable and require substantial and undue experimentation.

Amount of guidance provided. There is no substantial guidance provided as to what gene(s) combination would necessarily correlate with "modulation" of inflammatory diseases in general or more particularly, glomerulonephritis disease. The specification prophetically suggests that neutrophils' expression profiles from a normal subject and a patient suffering from an inflammatory disease can be compared. However, there does not appear to be any actual guidance provided as to what gene(s) would necessarily correlate to "modulation" of an inflammatory disease.

Number of working examples. There do not appear to be any substantially relative examples provided. The specification provides an example of neutrophils (isolated from a normal subject) treated with virulent and avirulent bacteria, with subsequent comparison of gene expression profiles. (e.g. Spec., p. 26, Example 2). However, this example actually uses neutrophils from a normal donor, thus would not be relative to inflammatory diseases generally or glomerulohenpritis, specficially.

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of working examples, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention.

Conclusion

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GERRY LEFFERS
PRIMARY EXAMINER